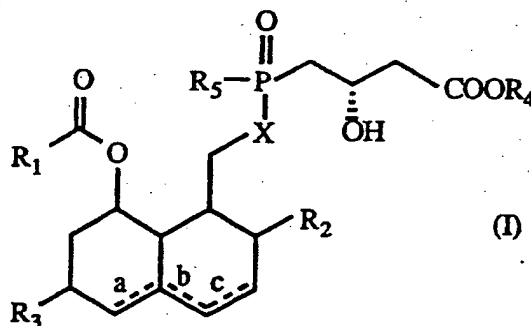




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/GB92/02226 (22) International Filing Date: 1 December 1992 (01.12.92) (30) Priority data: 9126144.6 10 December 1991 (10.12.91) GB (71) Applicant (for all designated States except US): BRITISH BIO-TECHNOLOGY LIMITED [GB/GB]; Watlington Road, Cowley, Oxford OX4 5LY (GB). (72) Inventors; and (75) Inventors/Applicants (for US only) : LEWIS, Christopher, Norman [GB/GB]; DAVIDSON, Alan, Hornsby [GB/GB]; ALLANSON, Nigel, Mark [GB/GB]; British Bio-technology Ltd, Watlington Road, Cowley, Oxford OX4 5LY (GB).		(74) Agent: WALLS, Alan, James; British Bio-Technology Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB).  (81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  Published With international search report.

(54) Title: 3-CARBOXY-2-HYDROXY-PROPANE-PHOSPHONIC ACID DERIVATIVES



## (57) Abstract

Compounds of general formula (I), wherein R<sub>1</sub> represents a C<sub>1-8</sub> alkyl, C<sub>3-8</sub> cycloalkyl, C<sub>3-8</sub> cycloalkyl(C<sub>1-8</sub>)alkyl, C<sub>2-8</sub> alkenyl, optionally C<sub>1-6</sub> alkyl substituted phenyl, or optionally substituted phenyl(C<sub>1-6</sub> alkyl) group; R<sub>2</sub> represents C<sub>1-8</sub> alkyl group; R<sub>3</sub> represents a C<sub>2-6</sub> alkenyl group or a C<sub>2-6</sub> alkenyl group linked to an optionally substituted phenyl group; R<sub>4</sub> represents a hydrogen atom, a C<sub>1-5</sub> alkyl group, a C<sub>1-5</sub> alkyl group substituted with a group chosen from optionally substituted phenyl, dimethylamino or acetyl amino; or a group M; R<sub>5</sub> represents a hydroxyl, -OM, or a C<sub>1-8</sub> alkoxy group; M represents a cation capable of forming a pharmaceutically acceptable salt; X represents an oxygen atom, NH group or CH<sub>2</sub> group; a, b and c represent independently single or double bonds except that when a or c are double bonds then b represents a single bond; or pharmaceutically or veterinarily acceptable acid addition salts or hydrates thereof are potent inhibitors of HMG-CoA and are useful in the treatment or prevention of hypercholesterolaemia, hyperlipoproteinaemia and arteriosclerosis.

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1        3-Carboxy-2-hydroxy-propane-phosphonic acid derivatives.

2  
3        Coronary heart disease (CHD) is a major cause of death  
4        and disability in the Western World. Epidemiological  
5        evidence strongly indicates that hypercholesterol-  
6        aemia - or more accurately, elevated levels of low-  
7        density lipoprotein cholesterol (LDL-C) - is a major  
8        risk factor for the development of CHD. Most  
9        cholesterol is synthesised de novo in the human body,  
10       in a multi-step process starting with acetyl-coenzyme  
11       A. The rate limiting step on this pathway is regulated  
12       by the enzyme 3-hydroxy-3-methyl glutaryl coenzyme A  
13       reductase (HMG-CoA reductase) which catalyses the  
14       conversion of HMG-CoA to mevalonic acid. The enzyme is  
15       therefore a prime target for pharmacological interven-  
16       tion for the control of hypercholesterolaemia.

17  
18       The present invention relates to novel 4-phosphono-3-  
19       hydroxy butanoic acid derivatives which inhibit the  
20       action of 3-hydroxy-3-methylglutaryl-coenzyme A  
21       reductase (HMG CoA reductase) and as such are useful in  
22       inhibiting cholesterol biosynthesis, and also relates  
23       to hypercholesterolemic compositions containing these  
24       compounds.

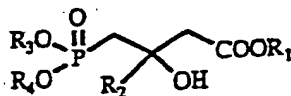
25  
26       FR-A-2596393 (Sanofi SA) discloses 3-carboxy-2-  
27       hydroxy-propane-phosphonic acid derivatives including  
28       salts thereof which are useful as hypolipaeic agents  
29       and have the formula:

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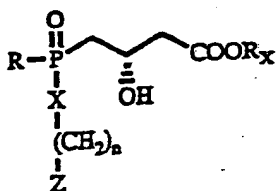
wherein

$\text{R}_1$  and  $\text{R}_2$  = H, lower alkyl or optionally substituted aryl or arylalkyl;

$\text{R}_3$  and  $\text{R}_4$  = H, lower alkyl or optionally substituted aryl or arylalkyl.

These compounds are reported to give greater reduction in cholesterol, triglyceride and phospholipid levels than meglutol.

DE-A-3817375 and US-A-4904646 (Squibb) disclose other 3-carboxy-2-hydroxy phosphonic acid derivatives and salts thereof as hypercholesterolemic agents having the formula:



1 wherein

2

3  $R_x$  is H, or alkyl;

4

5 R is OH, lower alkoxy or lower alkyl;

6

7 n is 1 or 2;

8

9 X is O, NH or  $CH_2$ ,

10

11 Z is a hydrophobic anchor, specifically an  
12 optionally substituted aryl, an optionally  
13 substituted naphthyl, or a decalin radical of  
14 general formula:

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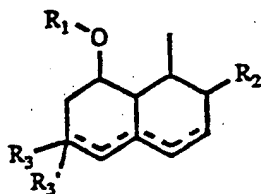
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$R_1$  = optionally substituted ester or ether

$R_2$  = lower alkyl

$R_3, R_3'$  = independently H, OH, lower alkyl,  
alkylaryl, aryl.

No biological data is given describing the potency of  
these compounds. Compounds containing an  $R_3$  alkenyl  
substituent are not described or claimed in these

1 documents.

2

3 Our copending application WO-A-9100280 discloses  
4 hypercholesterolemic agents of formula:

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15 wherein

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17  $R_1$  is alkyl, alkylaryl or aryl;

18

19  $R_2$  is H or lower alkyl;

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21  $R_3$  is  $C_{2-6}$  alkenyl optionally substituted with an  
22 optionally substituted aryl moiety;

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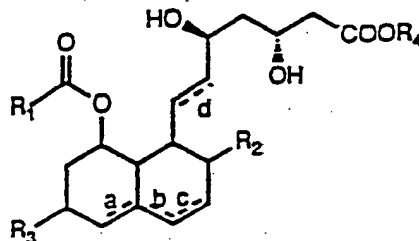
24  $R_4$  is H, lower alkyl, a pharmaceutically  
25 acceptable salt or an internal  $\delta$ -lactone;

26

27 a, b, c and d are single or double bonds except  
28 that when a or c is double then b is single.

29

30 This document discloses that introduction of certain  $R_3$   
31 alkenyl substituents increases the HMG CoA reductase.  
32 inhibitory activity of these compounds relative to  
33 mevinolin in which  $R_3$  is methyl.



1 Compounds which incorporate both  $R_3$  alkenyl  
2 substituents on the decalin and a phosphonyl group in  
3 the glutaryl-like side-chain are new. The present  
4 invention provides these novel decalin-based compounds  
5 which are potent inhibitors of the enzyme 3-hydroxy-3-  
6 methylglutaryl coenzyme A (HMG-CoA) reductase and  
7 therefore are useful in the treatment or prevention of  
8 hypercholesterolaemia, hyperlipoproteinaemia and  
9 arteriosclerosis, particularly atherosclerosis.

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11 According to the first aspect of the invention, there  
12 is provided a compound of general formula I

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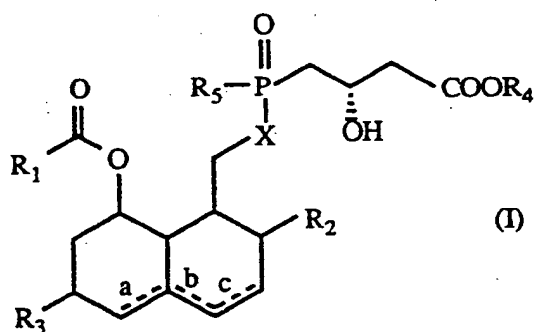
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wherein

$R_1$  represents a  $C_{1-8}$  alkyl,  $C_{3-8}$  cycloalkyl,  $C_{3-8}$  cycloalkyl( $C_{1-8}$ )alkyl,  $C_{2-8}$  alkenyl, optionally  $C_{1-6}$  alkyl substituted phenyl, or optionally substituted phenyl( $C_{1-6}$  alkyl) group;

$R_2$  represents  $C_{1-8}$  alkyl group;

$R_3$  represents a  $C_{2-6}$  alkenyl group or a  $C_{2-6}$  alkenyl group linked to an optionally substituted phenyl group;

1         $R_4$  represents a hydrogen atom, a  $C_{1-5}$  alkyl group,  
2        or a  $C_{1-5}$  alkyl group substituted with a group  
3        chosen from optionally substituted phenyl,  
4        dimethylamino or acetylamino or a group M;

5  
6         $R_5$  represents a hydroxyl, -OM, or a  $C_{1-8}$  alkoxy  
7        group;

8  
9        M represents a cation capable of forming a  
10        pharmaceutically acceptable salt;

11  
12        X represents an oxygen atom, NH group or  $CH_2$   
13        group;

14  
15        a, b and c represent independently single or  
16        double bonds except that when a or c are double  
17        bonds then b represents a single bond;

18  
19        or a pharmaceutically or veterinarily acceptable acid  
20        addition salt or hydrate thereof.

21  
22        As used herein, the term " $C_{1-8}$  alkyl" refers to  
23        straight chain or branched chain hydrocarbon groups  
24        having from one to eight carbon atoms. Illustrative of  
25        such alkyl groups are methyl, ethyl, propyl, isopropyl,  
26        butyl, isobutyl, sec-butyl, tert-butyl, pentyl,  
27        neopentyl, hexyl, heptyl and octyl.

28  
29        As used herein, the term " $C_{1-5}$  alkyl" refers to a  
30        straight chain or branched chain hydrocarbon group  
31        having from one to five carbon atoms. Illustrative of  
32        such groups are methyl, ethyl, propyl, isopropyl,  
33        butyl, isobutyl, sec-butyl, tert-butyl and pentyl.

1 As used herein, the term "C<sub>1-6</sub> alkyl" refers to a  
2 straight chain or branched chain hydrocarbon group  
3 having from one to six carbon atoms. Illustrative of  
4 such groups are methyl, ethyl, propyl, isopropyl,  
5 butyl, isobutyl, sec-butyl, tert-butyl, pentyl and  
6 hexyl.

7  
8 As used herein, the term C<sub>2-8</sub> alkenyl refers to  
9 straight chain or branched chain hydrocarbon groups  
10 having from two to eight carbon atoms and having in  
11 addition one or more double bonds, of either E or Z  
12 stereochemistry where applicable. This term would  
13 include for example vinyl, (E)-prop-1-enyl,  
14 (Z)-prop-1-enyl, but-3-enyl, (E)-1-methylpent-1-enyl,  
15 5-hexenyl and oct-7-enyl.

16  
17 The term "C<sub>2-6</sub> alkenyl" refers to a straight chain or  
18 branched chain hydrocarbon moiety having two to six  
19 carbon atoms and possessing an E or Z double bond.  
20 This includes for example, vinyl, (E)-prop-1-enyl,  
21 (Z)-prop-1-enyl, but-3-enyl, (E)-1-methylpent-1-enyl,  
22 and 5-hexenyl. Cognate terms (such as "C<sub>2-6</sub>" alkenoxy)  
23 are to be construed accordingly.

24  
25 The term "C<sub>3-8</sub> cycloalkyl" refers to a saturated  
26 alicyclic moiety having from 3 to 8 carbons arranged in  
27 a ring and includes, for example, cyclopropyl, cyclo-  
28 butyl, cyclopentyl, and cyclooctyl.

29  
30 The term "optionally substituted phenyl group" means  
31 substituted with up to four substituents each of which  
32 may be C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, hydroxy, thiol, amino,  
33 halo, (including fluoro, chloro, bromo, and iodo),

1 trifluoromethyl or nitro.

2

3 As used herein, the term "C<sub>1-6</sub> alkoxy" refers to  
4 straight chain or branched chain alkoxy groups having  
5 from one to six carbon atoms. Illustrative of such  
6 alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy,  
7 butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy,  
8 neopentoxy and hexoxy.

9

10 The phrase "a pharmaceutically acceptable salt" as used  
11 herein and in the claims is intended to include  
12 non-toxic alkali metal salts such as sodium, potassium,  
13 calcium and magnesium, the ammonium salt and salts with  
14 non-toxic amines such as trialkylamines, dibenzylamine,  
15 and other amines which have been or can be used to form  
16 salts of carboxylic and phosphonic acids.

17

18 In compounds of this invention, the presence of several  
19 asymmetric carbon atoms gives rise to diastereoisomers,  
20 each of which consists of two enantiomers, with the  
21 appropriate R or S stereochemistry at each chiral  
22 centre. The invention is understood to include all  
23 such diastereoisomers, their optically active  
24 enantiomers and mixtures thereof. The phosphorus atom  
25 forms an additional chiral centre and the invention  
26 includes both diastereoisomers at the phosphorus atom.

27

28 Disregarding any asymmetric centres which might be  
29 present in substituents R<sub>1-6</sub>, the preferred relative  
30 and absolute stereochemistry is as shown in the  
31 structure below. The Cahn, Ingold, Prelog designations  
32 for this compound are 1S, 2S 4aR, 6S, 8S, 8aS, and 3'S.  
33 Both diastereomers at phosphorus are equally preferred.

1 It should be noted that the preferred diastereomers of  
2 other compounds of the invention may differ in their  
3 R-S designations because of the manner in which the  
4 sequence rules are determined.

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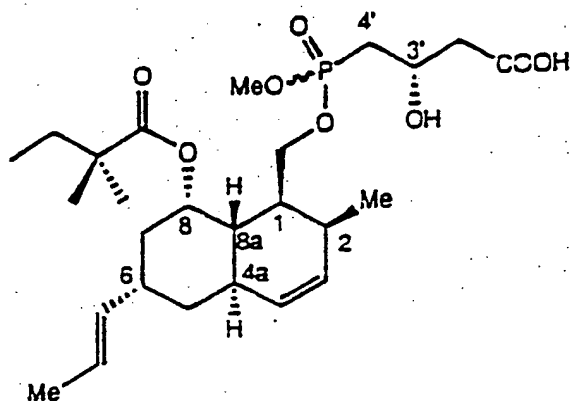
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Clearly in compounds in which a or b (in the general formula) are double bonds, the carbon atom labelled C<sub>4a</sub> will not be an asymmetric centre.

Preferred compounds include those in which independently or in any combination:

R<sub>1</sub> represents a C<sub>1-5</sub> branched chain alkyl group;

R<sub>2</sub> represents methyl or ethyl;

R<sub>3</sub> is E-1-propenyl;

R<sub>5</sub> represents a hydroxy or a C<sub>1-5</sub> alkoxy group;

c or a and c are double bonds;

1 X is oxygen or an NH group.

2

3 Examples of this preferred group are:

4

5 4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2,4a,5,6,7,8,8a  
6 octahydro-2-methyl-8-[(2"-dimethyl-1"oxobutyl)-oxy]-  
7 6-[(E)-prop-1-enyl]-1-naphthalenyl)methyleneoxy]  
8 phosphonyl-3'-hydroxybutanoic acid;

9

10 4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2,4a,5,6,7,8,8a  
11 octahydro-2-methyl-8-[(2"-dimethyl-1"oxobutyl)-oxy]-  
12 6-[(E)-prop-1-enyl]-1-naphthalenyl)methyleneoxy](R and  
13 S) methoxyphosphonyl-3'-hydroxybutanoic acid;

14

15 4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2,4a,5,6,7,8,8a  
16 octahydro-2-methyl-8-[(2"-dimethyl-1"-oxobutyl)-oxy]-  
17 6-[(E)-prop-1-enyl]-1-naphthalenyl)methyleneamino]  
18 phosphonyl-3'-hydroxybutanoic acid,

19

20 or salts, particularly lithium salts, thereof.

21

22 Compounds of general formula I may be prepared by any  
23 suitable method known in the art and/or by the  
24 following process, which itself forms part of the  
25 invention.

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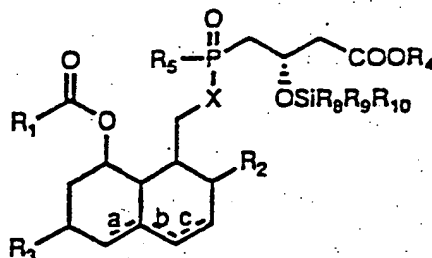
27 According to a second aspect of the invention, there is  
28 provided a process for preparing a compound of general  
29 formula I as defined above, the process comprising:

30

31 (a) deprotecting a compound of general formula II

32

33



II

wherein,

$R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $X$ ,  $a$ ,  $b$  and  $c$  are as are as defined for general formula I; and

$R_8$ ,  $R_9$  and  $R_{10}$  independently comprise  $C_{1-8}$  alkyl or phenyl;

using a nucleophilic desilylating agent;

(b) optionally after step (a), converting a compound of general formula I to another compound of general formula I.

Examples of suitable nucleophilic reagents for use in step (a) are sources of fluoride ions such as tetrabutylammonium fluoride in an inert solvent such as tetrahydrofuran and hydrofluoric acid in aqueous acetonitrile. With both these reagents, the reaction is preferably carried out at ambient temperature and when tetrabutylammonium fluoride is used as the

1 reagent, the reaction should be carried out in an inert  
2 atmosphere, for example nitrogen or argon and in the  
3 presence of an organic acid buffer such as acetic acid.  
4 However, other methods for the removal of silyl  
5 protecting groups are known and any of these may also  
6 be used.

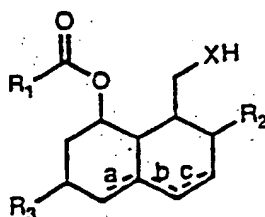
7  
8 A compound of general formula I in which either or both  
9  $R_4$  or  $R_5$  is an alkyl group can be converted to a  
10 compound in which both  $R_4$  and  $R_5$  are hydrogen atoms by  
11 hydrolysis using at least a 2-fold excess of a base.  
12 Any base can be used but hydroxylic bases such as  
13 lithium, sodium or potassium hydroxides or metal alkyl  
14 thiolates such as lithium or sodium methyl thiolate or  
15 sodium phenyl thiolate are particularly suitable.

16  
17 The reaction temperature may be from 50°C to 80°C and  
18 any solvent may be used which boils at a temperature at  
19 least as high as the required reaction temperature and  
20 which dissolves both the starting material and the  
21 base. Suitable solvents include polar organic solvents  
22 such as methanol, ethanol, tetrahydrofuran,  
23 acetonitrile N,N-dimethylformamide, alone or mixed with  
24 water, or water itself. The hydrolysis is allowed to  
25 continue for at least twelve hours.

26  
27 Compounds of general formula I in which both  $R_4$  and  $R_5$   
28 are alkyl groups can be selectively hydrolysed to give  
29 compounds of general formula I in which  $R_4$  is a  
30 hydrogen atom and  $R_5$  is an alkyl group by mild  
31 hydrolysis with one of the bases mentioned above,  
32 although in this case, there should not be an excess  
33 amount of base. The polar organic solvents mentioned

1 above are also suitable for this mild hydrolysis  
 2 reaction but the reaction temperature should be between  
 3 0°C and 50°C, preferably ambient temperature. The  
 4 reaction proceeds to completion in about twelve hours.

5  
 6 Silyl ethers of general formula II wherein X is O or NH  
 7 can be prepared by reaction of a compound of general  
 8 formula III

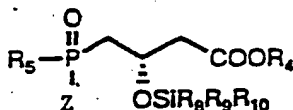


III

16  
 17  
 18  
 19  
 20 wherein

21  
 22 X is O or NH and

23  
 24 R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, a, b and c are as defined in general  
 25 formula I; with a compound of general formula IV



IV

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 33 wherein R<sub>4</sub> and R<sub>5</sub> are as defined in general formula I;

1  $R_8$ ,  $R_9$  and  $R_{10}$  are as defined in general formula II;  
2 and

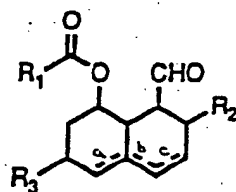
3  
4 Z is hydroxy, fluoro, chloro or bromo.

5  
6 When Z is fluoro, chloro or bromo, the reaction should  
7 be carried out under an inert atmosphere, for example  
8 nitrogen or argon, preferably at ambient temperature.  
9 The solvent for this reaction is preferably inert and  
10 basic, for example pyridine, but inert non-basic  
11 organic solvents such as dichloromethane or  
12 tetrahydrofuran may also be used although in this case,  
13 a mild organic base such as triethylamine or N-methyl  
14 morpholine must also be present.

15  
16 When Z is a hydroxy group, the compounds of general  
17 formula II may be prepared by reaction of compounds of  
18 general formulae III and IV together with a condensing  
19 agent, for example dicyclohexanecarbodiimide (DCC) or  
20 water soluble derivatives thereof. In this case, the  
21 reaction should preferably be carried out in an inert  
22 solvent such as dichloromethane, tetrahydrofuran or  
23 pyridine. In place of DCC, it is possible to use other  
24 condensing agents such as carbonyldiimidazole.

25  
26 Compounds of general formula IV are known and can be  
27 prepared by the method described in DE-A-3817375.  
28 Compounds of general formula III in which X is O are  
29 known and compounds of general formula III wherein X is  
30 NH can be prepared from compounds of general formula V

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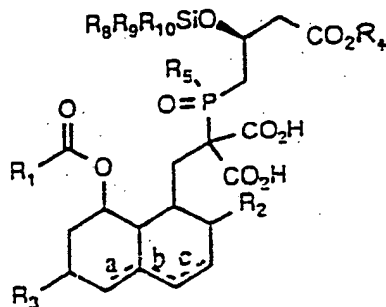
V

wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $a$ ,  $b$  and  $c$  are as defined for general formula I;

by the method described in DE-A-3817375.

Compounds of general formula V are also known.

Compounds of general formula II wherein X is  $\text{CH}_2$  can be prepared by decarboxylation of compounds of general formula VI



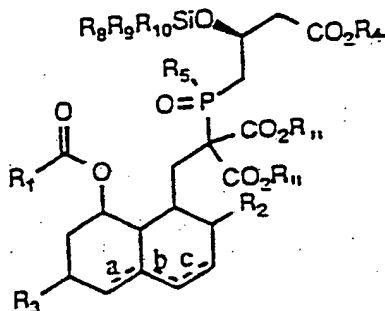
VI

wherein

1 a, b, c, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>8</sub>, R<sub>9</sub>, and R<sub>10</sub> are as defined  
 2 above and R<sub>5</sub> is a C<sub>1-8</sub> alkoxy group.

3  
 4 The decarboxylation reaction may be performed by any  
 5 method known in the art, but preferred methods include  
 6 heating a compound of general formula VI to a  
 7 temperature of greater than 70°C in an inert,  
 8 non-basic, relatively high-boiling solvent such as  
 9 water, DMSO or DMF. The solvent may optionally contain  
 10 ionic solutes for example alkali metal halides (eg  
 11 sodium chloride in DMSO) or sodium bicarbonate (in DMF)  
 12 which are known to promote decarboxylation reactions.

13  
 14 Compounds of general formula VI can be obtained by  
 15 hydrolysis of compounds of general formula VII



VII

24  
 25 wherein

26  
 27 a, b, c, R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>8</sub>, R<sub>9</sub> and R<sub>10</sub> are as  
 28 defined above;

29  
 30 R<sub>5</sub> is a C<sub>1-8</sub> alkoxy group; and

31  
 32 each R<sub>11</sub> independently represents a hydrogen atom, a  
 33 C<sub>1-5</sub> alkyl (optionally substituted phenyl) group or the

1 two  $R_{11}$  groups may, together with the atoms to which  
2 they are attached, form a  $C_{6-8}$  cyclic system, for  
3 example an isopropylidene diester as in mel drums acid.

4  
5 For the hydrolysis, any combination of base and solvent  
6 that is suitable for the hydrolysis of esters may be  
7 used, but preferred systems include lithium, sodium or  
8 potassium hydroxides or metal alkyl thiolates such as  
9 lithium or sodium methylthiolates or sodium phenyl  
10 thiolate. The reaction may be performed in a solvent  
11 which dissolves both the base and the substrate. Polar  
12 organic solvents are suitable for this purpose for  
13 example methanol, ethanol, THF acetonitrile, DMF or  
14 DMSO, alone or mixed with water or water itself.  
15 Optionally if  $R_{11}$  is an acid sensitive grouping such as  
16 a t-butyl ester, then acid hydrolysis methods such as  
17 are known in the art may be employed.

18

19 Compounds of general formula VII can be obtained by  
20 reaction of a compound of general formula VIII

21

22

23

24

25

26

27

28

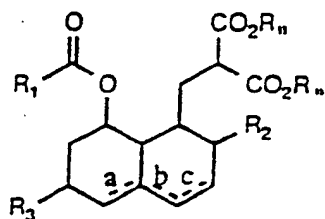
29

30 wherein

31

32 a, b, c,  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_{11}$  are as defined above;

33



VIII

1 with a compound of general formula X

2

3

4

5

6

7

8

9

10

11 wherein

12

13  $R_4$ ,  $R_8$ ,  $R_9$  and  $R_{10}$  are as defined above;

14

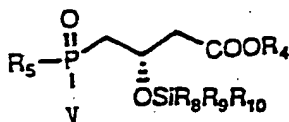
15  $R_5$  is a  $C_{1-8}$  alkoxy group;

16

17  $V$  is fluoro, chloro or bromo.

18

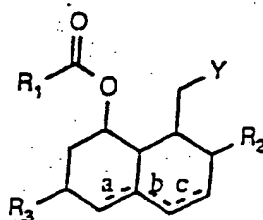
19 The reaction may be performed by addition of a strong  
20 non-nucleophilic base to a compound of general formula  
21 VIII in a polar aprotic solvent between  $-78^{\circ}\text{C}$  and  
22 ambient temperature to deprotonate the compound at a  
23 position alpha to the carboxylic ester groups. Once  
24 the malonate anion has been formed, a solution of a  
25 compound of general formula X in the same solvent is  
26 added to it between  $0^{\circ}\text{C}$  and ambient temperature, and  
27 the reaction mixture is heated at between 50 and  $100^{\circ}\text{C}$   
28 until the reaction is complete. Suitable bases for the  
29 first step include sodium alkyl lithium reagents,  
30 sodium and potassium hydride, secondary alkyl lithium  
31 amides such as lithium diisopropyl amide and sodium and  
32 lithium hexamethyl disilazides. THF, dimethoxyethyl  
33 ether, DMF and DMSO are preferred solvents for this



X

1 transformation although other solvents could also be  
2 used. Compounds of general formula X can be prepared  
3 by methods described in DE-A-3817375.

4  
5 Compounds of general formula VIII can be prepared from  
6 compounds of general formula IX



IX

7  
8  
9  
10  
11  
12  
13  
14  
15  
16 wherein a, b, c, R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> are as defined in  
17 general formula I and Y is a leaving group, for example  
18 a chloride, bromine, or iodine atom, or a mesylate,  
19 tosylate or triflate group;

20  
21 by reaction with an equivalent, or preferably an  
22 excess, of the anion of a malonic acid derivative in a  
23 suitable non-protic solvent.

24  
25 The malonic acid derivative can be a monoalkyl-, or  
26 dialkyl- or arylester of malonic acid, and cyclic  
27 diesters such as Meldrum's acid are also suitable.  
28 Lower alkyl diesters such as dimethyl and diethyl  
29 malonate lower alkyl monoesters such as monomethyl-,  
30 monoethyl- and mono-t-butyl- malonic acid are preferred  
31 since these reagents react more quickly and in higher  
32 yield.

33

1 The reaction is performed by addition of a strong  
2 non-nucleophilic base to a solution of the malonate  
3 compound in a non-protic solvent. For diesters, one  
4 equivalent of base to each equivalent of malonate  
5 compound should be used, but for monoesters of malonic  
6 acid, two equivalents of base for each equivalent of  
7 substrate should be employed. The deprotonation may be  
8 performed between  $-78^{\circ}\text{C}$  and room temperature. Any base  
9 and solvent suitable for the deprotonation of compound  
10 VIII may be used for this step, although  
11 hexamethyldisilazide in THF is especially preferred.  
12 The reaction proceeds by adding a solution of a  
13 compound of general formula IX to a solution of the  
14 malonate anion in the same solvent and the reaction  
15 mixture is heated at between  $50$  and  $100^{\circ}\text{C}$  for at least  
16 5 hours.

17  
18 Compounds of general formula IX can be prepared from  
19 known compounds of general formula III where X is  
20 oxygen. Mesylates, tosylates and triflates of general  
21 formula IX may be prepared directly from alcohols of  
22 general formula III by reaction with the requisite  
23 sulphonyl chloride in a basic organic solvent such as  
24 pyridine or a non-protic solvent such as  
25 dichloromethane containing a mild organic base such as  
26 triethylamine at or below  $0^{\circ}\text{C}$ . Such transformations  
27 are known in the art. Halides of general formula IX  
28 may be prepared from these sulphonate esters by  
29 reactions also known in the art. For example an iodide  
30 of general formula IX may be prepared from the mesylate  
31 by heating it under reflux in methyl ethyl ketone  
32 containing 5 equivalents of sodium iodide for 18 hours.  
33

1 Compounds of general formula II are valuable  
2 intermediates in the preparation of compounds of  
3 general formula I and therefore according to a third  
4 aspect of the invention, there is provided a compound  
5 of general formula II.

6  
7 The compounds of general formula I are useful as anti-  
8 hypercholesterolaemic agents for the treatment of  
9 arteriosclerosis, hyperlipidaemia, familial hyperchol-  
10 esterolaemia and like diseases in humans. The  
11 invention therefore also relates to a method for the  
12 treatment of patients suffering from these diseases.

13  
14 According to a further aspect of the invention there is  
15 provided a compound of general formula I for use in  
16 human or veterinary medicine, particularly in the  
17 treatment or prophylaxis of hypercholesterolaemia,  
18 hyperlipidaemia or arteriosclerosis.

19  
20 According to yet a further aspect of the invention,  
21 there is provided the use of a compound of general  
22 formula I in the preparation of an agent for the  
23 treatment or prophylaxis of hypocholesterolaemia,  
24 hyperlipidaemia or arteriosclerosis.

25  
26 Compounds of general formula I may be administered  
27 orally or parenterally in the form of a capsule, a  
28 tablet, an injectable preparation or the like. It is  
29 usually desirable to use the oral route. Doses may be  
30 varied, depending on the age, severity, body weight and  
31 other conditions of human patients but daily dosage for  
32 adults is within a range of from about 2 mg to 2000 mg  
33 (preferably 5 to 100 mg) which may be given in one to

1 four divided doses. Higher doses may be favourably  
2 employed as required.

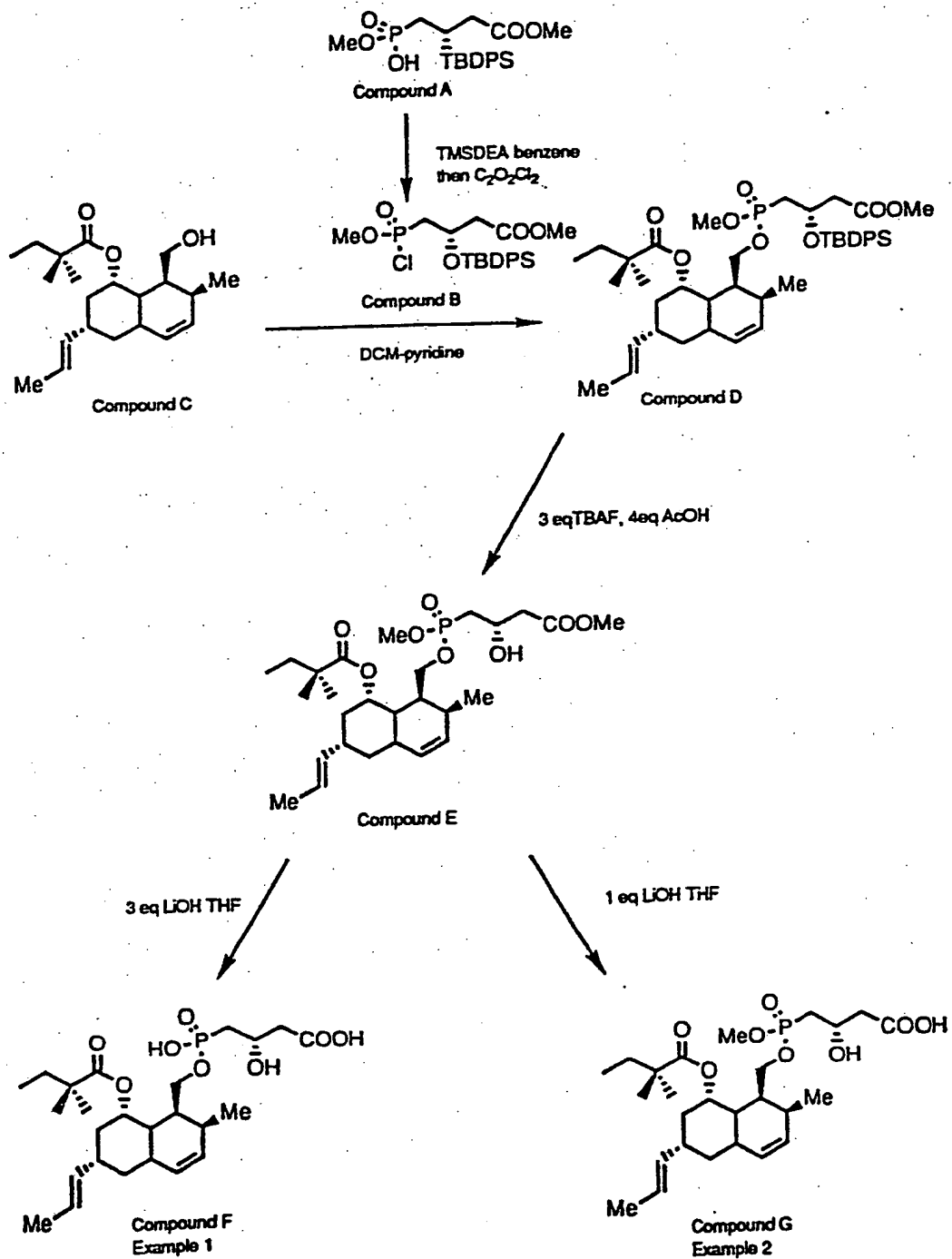
3  
4 The compounds of this invention may also be  
5 co-administered with pharmaceutically acceptable non  
6 toxic cationic polymers capable of binding bile acids  
7 in a non-reabsorbable form in the gastrointestinal  
8 tract. Examples of such polymers include  
9 cholestyramine, colestipol and  
10 poly[methyl-(3-trimethylaminopropyl)-iminotrimethylene  
11 dihalide]. The relative amounts of the compounds of  
12 this invention and these polymers is between 1:100 and  
13 1:15000.

14  
15 The following examples show representative compounds  
16 encompassed by this invention and their syntheses (see  
17 Scheme 1). However, it should be understood that they  
18 are for the purposes of illustration only.

19  
20 Organic solutions were dried over sodium sulphate or  
21 magnesium sulphate, and evaporated under reduced  
22 pressure. NMR spectra were recorded at ambient  
23 temperature in deuteriochloroform at 250 MHz for proton  
24 and 62.5 MHz for carbon unless noted otherwise. All  
25 chemical shifts are given in parts per million relative  
26 to tetramethylsilane. Infra red spectra were recorded  
27 at ambient temperature in solution in chloroform, or in  
28 the solid state in a potassium bromide disc as noted.

29  
30 Chromatography was carried out using Woelm 32-60  $\mu$ m  
31 silica.

32  
33

Scheme 1

Example 1Step A

Methyl-(S)-3[1,1-dimethylethyl]-diphenylsilyloxy]-4-  
(chloromethoxyphosphinyl)-butanoate.  
[compound B]

A stirred solution of methyl-(S)-3[(1,1-Dimethylethyl)-diphenylsilyloxy]-4-(hydroxymethoxyphosphinyl)-butanoate [compound A] (1.16 g, 2.56 mmol) (prepared by the method of DE-A-3817375) in 1:1 dry benzene (5 ml) and dichloromethane (5ml) was treated with trimethylsilyldiethylamine (1.16 ml, 6.1 mmol) at room temperature under argon. After 1 hr the solvent was evaporated under reduced pressure and the residue taken up in dichloromethane (5ml) containing 2 drops of DMF. The solution was cooled to -15°C and treated with oxalyl chloride (292 µl, 3.34 mmol). After 5 min at -15°C, the solution was allowed to warm to room temperature over 1 hr and then evaporated under reduced pressure to give crude methyl-(S)-3[1,1-dimethylethyl]-diphenylsilyloxy]-4-(chloromethoxyphosphinyl)-butanoate [compound B] (1.10 g) as a yellow oil.

Step B

Methyl-4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2,4a,5,6,7,8,8a  
octahydro-2-methyl-8-[(2"-dimethyl-1"oxobutyl)-oxy]-  
6[(E)-prop-1-enyl]-1-naphthalenyl)methyleneoxy]methoxy-  
phosphinyl-3'[1,1-dimethylethyl]-diphenylsilyloxy]-  
butanoate.  
[compound D]

Crude phosphinyl chloride [compound B] (234mg, 0.496 mmol) was added in three portions of 115, 60 and 60mg

1 after 0, 15 and 40 hr respectively, to a stirred  
2 solution of (1S,2S,4aR,6S,8S,8aS)(1,2,4a,5,6,7,8,8a  
3 octahydro-2-methyl-8-[(2"-dimethyl-1"oxo-butyl)-oxy]-6-  
4 [(E)-prop-1-enyl]-1-naphthalenyl)methanol [compound C]  
5 (50 mg, 0.149 mmol) (prepared by the method of patent  
6 WO-A-9100280) in 2:1 pyridine-dichloromethane (0.5 ml)  
7 at room temperature under argon. After 3 days the  
8 reaction mixture was diluted with dichloromethane (25  
9 ml) and washed twice with 3N citric acid solution (2x20  
10 ml). Drying over MgSO<sub>4</sub> and evaporation under reduced  
11 pressure gave a clear oil (240 mg) which was flash  
12 chromatographed on silica (8 g) under gradient elution  
13 [1:4 ethyl acetate-hexane to 2:3 ethyl acetate-hexane]  
14 to afford methyl-4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2,  
15 4a,5,6,7,8,8a octahydro-2-methyl-8-[(2"-dimethyl-  
16 1"oxobutyl)-oxy]-6-[(E)-prop-1-enyl]-1-naphthalenyl)  
17 methyleneoxy]methoxy-phosphinyl-3'[1,1-dimethylethyl)-  
18 diphenylsilyloxy]-butanoate [compound D] (37 mg, 0.052  
19 mmol, 35% yield) as an oil.

20

21 TLC 40% ethyl acetate-hexane R<sub>f</sub> = 0.25 U.V. and PMA.

22

23

#### 24 Step C

25 Methyl-4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2, 4a,  
26 5,6,7,8,8a octahydro-2-methyl-8-[(2"-dimethyl-  
27 1"oxobutyl)-oxy]-6-[(E)-prop-1-enyl]-1-naphthalenyl)  
28 methyleneoxy]methoxyphosphinyl-3'-hydroxy-butanoate.  
29 [compound E]

30

31 The silyl ether [compound D] (74 mg, 0.096 mmol) was  
32 stirred for 18hr at room temperature under argon in a  
33 solution of dry THF (1.2 ml) containing tetrabutyl-

1 ammonium fluoride (0.29 mmol) and acetic acid (0.38  
2 mmol). The reaction mixture was diluted with diethyl  
3 ether (20 ml) and washed with water (20 ml) then  
4 saturated sodium carbonate solution (20 ml) and dried  
5 over MgSO<sub>4</sub>. Flash chromatography of the concentrated  
6 residue using 1:1 ethyl acetate-hexane increasing to  
7 ethyl acetate gave the title compound as an oil.

8  
9 Yield (29 mg, 0.055 mmol) 61%

10  
11 TLC Ethyl acetate R<sub>f</sub> 0.38

12  
13  $\delta$ H (CDCl<sub>3</sub>) 0.84(3H, t, J 7.3 Hz); 0.94(3H, d, J 6.4  
14 Hz); 1.16(6H, 2s); 1.17-2.17(14H, m); 3.71(3H total - 2  
15 isomers at phosphorus, 2d, J 10.9 Hz); 3.73-4.4(7H, m);  
16 5.6-5.8(2H, m).

17  
18  $\delta$ C (CDCl<sub>3</sub>) 176.8, 176.2, 134.6, 130.9, 121.6, 68.0,  
19 63.4, 62.8, 51.3, 42 approx, 41.5, 38.1, 36.4, 36.3,  
20 35.8, 34.5, 33.8, 31.5, 29.9, 29.7, 29.5, 23.2, 16.5,  
21 14.3, 14.0, 11.1, 7.8.

22  
23 Example 2

24  
25 4'-[1S,2S,4aR,6S,8S,8aS,3'S,](1,2,4a,5,6,7,  
26 8,8a octahydro-2-methyl-8-[(2"-dimethyl-1"oxobutyl)-  
27 oxy]-6-[(E)-prop-1-enyl]-1-naphthalenyl) methyleneoxy]-  
28 phosphonyl-3'-hydroxy-butanoic acid.

29 [compound F]

30  
31 Compound E from Example 1 (14.5 mg,  $2.9 \times 10^{-5}$ M) was  
32 heated at 50°C for 16 hr with three equivalents of  
33 lithium hydroxide (2 mg,  $8.7 \times 10^{-5}$ M) in THF (1.1 ml).

1 The crude reaction mixture was chromatographed on two  
2 analytical 1mm kieselgel 60 plates (elution with 7:3  
3 isopropanol-  $\text{NH}_4\text{OH}_{\text{aq}}$ ) to give the title compound as an  
4 oil (7 mg,  $1.4 \times 10^{-5}\text{M}$ ).

5

6 Yield 48%.

7

8 TLC eluant 7:3 i-PrOH: $\text{NH}_4\text{OH}_{\text{aq}}$  Rf = 0.51 U.V. only.

9

10  $\delta\text{H}$  ( $\text{CDCl}_3$ ) 0.95(6H, s); 1.2-2.1(19H, m); 3.8(1H, m);  
11 4.4(3H, m); 5.05-5.8(5H, m).

12

13 Example 3

14

15 4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2,4a,5,6,7,  
16 8,8a octahydro-2-methyl-8-[(2"-dimethyl-1"oxobutyl)-  
17 oxy]-6-[(E)-prop-1-enyl]-1-naphthalenyl) methyleneoxy]-  
18 R and S-methoxyphosphinyl-3'-hydroxybutanoic acid.  
19 [compound G]

20

21 Compound E from Example 1 (14.5 mg,  $2.7 \times 10^{-5}\text{M}$  was  
22 stirred for 16 hr in tetrahydrofuran (0.4 ml)  
23 containing 1.2 equivalents of lithium hydroxide ( $3.5 \times$   
24  $10^{-5}\text{M}$ ). The neat solution was thin-layer  
25 chromatographed on two 10 x 20 cm Kieselgel 60  
26 analytical plates eluting with 7:3 isopropanol-2N  
27 aqueous ammonia solution to give the desired compound  
28 as an oil (13 mg,  $2.5 \times 10^{-5}\text{M}$ ).

29

30 Yield 93%.

31

32 TLC eluant 7:3 i-PrOH: $\text{NH}_4\text{OH}_{\text{aq}}$  Rf 0.68.

33

1  $\delta$ H (CDCl<sub>3</sub>) 0.84(3H, t, J 7.3Hz); 0.94(3H, d, J 6.4Hz);  
2 1.16(6H, 2s); 1.17-2.17(14H, m); 2.5(4H, m); 3.71(3H  
3 total, 2d, J 10.9Hz for each POME); 3.73-4.4(7H, m);  
4 5.60-5.8(2H, m).

5  
6  $\delta$ C (CDCl<sub>3</sub>) 176.8, 176.2, 134.6, 130.9, 121.6, 68.0,  
7 63.4, 62.8, 51.3, 42 approx, 41.5, 38.1, 36.4, 36.3,  
8 35.8, 34.5, 33.8, 31.5, 29.9, 29.7, 29.5, 23.2, 16.5,  
9 14.3, 14.0, 11.1, 7.8.

10  
11 The intrinsic HMG-CoA reductase inhibition activity of  
12 the claimed compounds is measured in the in vitro  
13 protocols described below.

14  
15 Example 4 - Pharmacology

16  
17 IN VITRO DETERMINATION OF INHIBITORY POTENTIAL OF  
18 HMG-CoA REDUCTASE INHIBITORS.

19  
20 HMG-CoA reductase was induced in rats by feeding a  
21 normal diet supplement with 3% cholestyramine resin for  
22 one week prior to sacrifice. The livers were excised  
23 from the sacrificed rats and microsomal pellets  
24 prepared by the method of Kleinsek et al, Proc. Natl.  
25 Acad. Sci. USA, 74 (4), pp 1431-1435, 1977. Briefly,  
26 the livers were immediately placed in ice-cold buffer I  
27 (see below) and homogenised in a Potter-Elvehjem type  
28 glass/TEFLON homogeniser (10 passes at 1000 rpm). (The  
29 word TEFLON is a trade mark). The homogenate was  
30 centrifuged at 100,000 x g for 75 minutes, the  
31 microsomal pellet resuspended in buffer II (see below)  
32 and centrifuged at 100,000 x g for 75 minutes. The  
33 resultant pellet was stored at -70°C until required for

1 assay purposes. The compositions of buffers I and II  
2 are given below.

3  
4  
5 Buffer I

6 50 mM KPO<sub>4</sub> pH 7.0

7 0.2 M sucrose

8 2 mM DTT

Buffer II

50 mM KPO<sub>4</sub> pH 7.0

0.2 M sucrose

2mM DTT

50 mM EDTA

10  
11  
12 Assay of HMG-CoA Reductase Activity and Determination  
13 of Activity of Inhibitors

14  
15 Membrane bound enzyme isolated as above is used for  
16 determining the activity of inhibitors. The assay is  
17 performed in a total volume of 300 µL in 100 mM KPO<sub>4</sub> pH  
18 7.2 buffer, containing 3 mM MgCl<sub>2</sub>, 5 mM glucose-6-  
19 phosphate, 10 mM reduced glutathione, 1 mM NADP, 1 unit  
20 glucose-6-phosphate dehydrogenase, and 1 mg/mL BSA,  
21 with resuspended enzyme. Putative inhibitors are  
22 dissolved in dimethylsulphoxide and 10 µL aliquots  
23 added to the incubation.

24  
25 The assay is pre-incubated at 37°C for 10 minutes and  
26 initiated by the addition of 0.1 µCi 3-hydroxy-3-  
27 methyl-[3-<sup>14</sup>C]glutaryl coenzyme A (52 Ci/Mole) followed  
28 by incubating the complete reaction at 37°C for 10  
29 minutes. At the end of this period the reaction is  
30 stopped by adding 300 µL of a 10 mM mevalonolactone  
31 solution in 0.1 M hydrochloric acid and the mevalonic  
32 acid product allowed to lactonise for a further period  
33 of 30 minutes. The product is then isolated by

1 chromatography using Bio-Rex 5 resin and the enzyme  
2 activity quantified by liquid scintillation spectro-  
3 photometry.

4  
5 Appropriate controls are included in the assay and  $IC_{50}$   
6 values obtained by graphical means.

7  
8 Representative  $IC_{50}$  values for compounds F and G in the  
9 isolated enzyme assay were 11 and 2900 nanomoles  
10 respectively. In this assay, the  $IC_{50}$  value for  
11 dihydromevinolin was 30 nanomoles.

12  
13 Included within the scope of this invention is the  
14 method of treating arteriosclerosis, familial hyper-  
15 cholesterolaemia or hyperlipidaemia which comprises  
16 administering to a subject in need of such treatment a  
17 non toxic therapeutically effective amount of the  
18 compounds of formulae I or II or pharmaceutical  
19 compositions thereof.

20

21

22

23

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28

29

30

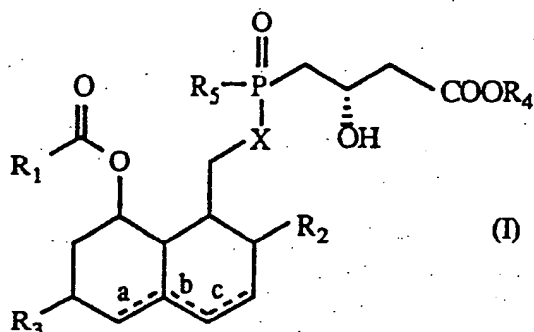
31

32

33

CLAIMS

1. A compound of general formula I:



wherein

$R_1$  represents a  $C_{1-8}$  alkyl,  $C_{3-8}$  cycloalkyl,  $C_{3-8}$  cycloalkyl( $C_{1-8}$ )alkyl,  $C_{2-8}$  alkenyl, optionally  $C_{1-6}$  alkyl substituted phenyl, or optionally substituted phenyl( $C_{1-6}$  alkyl) group;

$R_2$  represents  $C_{1-8}$  alkyl group;

$R_3$  represents a  $C_{2-6}$  alkenyl group or a  $C_{2-6}$  alkenyl group linked to an optionally substituted phenyl group;

$R_4$  represents a hydrogen atom, a  $C_{1-5}$  alkyl group, a  $C_{1-5}$  alkyl group substituted with a group chosen from optionally substituted phenyl, dimethyl amino or acetylamino; or a group M;

$R_5$  represents a hydroxyl, -OM, or  $C_{1-8}$  alkoxy group;

1 M represents a cation capable of forming a  
2 pharmaceutically acceptable salt;

3  
4 X represents an oxygen atom, NH group or CH<sub>2</sub>  
5 group;

6  
7 a, b and c represent independently single or  
8 double bonds except that when a or c are double  
9 bonds then b represents a single bond;

10  
11 or a pharmaceutically or veterinarily acceptable acid  
12 addition salt or hydrate thereof.

13  
14 2. A compound as claimed in claim 1 wherein R<sub>1</sub> is a  
15 C<sub>1-5</sub> branched chain alkyl group.

16  
17 3. A compound as claimed in claim 1 or claim 2  
18 wherein R<sub>2</sub> is a methyl or an ethyl group.

19  
20 4. A compound as claimed in any one of claims 1 to 3  
21 wherein R<sub>3</sub> is E-1-propenyl.

22  
23 5. A compound as claimed in any one of claims 1 to 4  
24 wherein R<sub>5</sub> is a hydroxy or a C<sub>1-5</sub> alkoxy group.

25  
26 6. A compound as claimed in any one of claims 1 to 5  
27 wherein c or a and c are double bonds.

28  
29 7. A compound as claimed in any one of claims 1 to 6  
30 wherein X is oxygen or an NH group.

31  
32 8. 4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2,4a,5,6,7,8,8a  
33 octahydro-2-methyl-8-[(2"-dimethyl-1"oxobutyl)-oxy]-6-

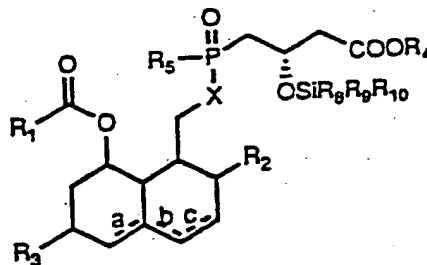
1 [(E)-prop-1-enyl]-1-naphthalenyl)methyleneoxy]phos-  
 2 phonyl-3'-hydroxybutanoic acid;

3  
 4 4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2,4a,5,6,7,8,8a  
 5 octahydro-2-methyl-8-[(2"-dimethyl-1"-oxobutyl)-oxy]-  
 6 6-[(E)-prop-1-enyl]-1-naphthalenyl)methyleneoxy](R and  
 7 S) methoxyphosphonyl-3'-hydroxybutanoic acid; or

8  
 9 4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2,4a,5,6,7,8,8a  
 10 octahydro-2-methyl-8-[(2"-dimethyl-1"-oxobutyl)-oxy]-  
 11 6-[(E)-prop-1-enyl]-1-naphthalenyl)methyleamino]  
 12 phosphonyl-3'-hydroxybutanoic acid.

13  
 14 9. A process for the preparation of a compound as  
 15 claimed in any one of claims 1 to 8, the process  
 16 comprising

17  
 18 (a) deprotecting a compound of general formula II



II

wherein

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and X are as defined in claim 1; and

1 R<sub>8</sub>, R<sub>9</sub> and R<sub>10</sub> independently comprise C<sub>1-8</sub> alkyl or  
2 phenyl;

3

4 with a nucleophilic desilylating agent;

5

6 (b) optionally after step (a) converting a compound of  
7 general formula I to another compound of general  
8 formula I.

9

10 10. A process as claimed in claim 9 wherein the  
11 nucleophilic deprotecting agent comprises a source of  
12 fluoride ions, for example tetrabutylammonium fluoride  
13 or hydrofluoric acid.

14

15 11. A compound as claimed in any one of claims 1 to 8  
16 for use in medicine.

17

18 12. The use of a compound as claimed in any one of  
19 claims 1 to 7 in the preparation of an agent for the  
20 treatment or prophylaxis of hypocholesterolemia,  
21 hyperlipidaemia or arteriosclerosis.

22

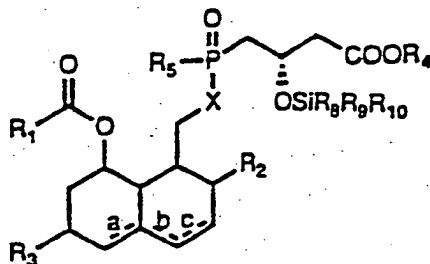
23 13. A pharmaceutical or veterinary composition  
24 comprising a compound as claimed in any one of claims 1  
25 to 8 together with a pharmaceutically or verterinarily  
26 acceptable excipient.

27

28 14. A composition as claimed in claim 13 further  
29 including at least one pharmaceutically acceptable  
30 non-toxic cationic polymer capable of binding bile  
31 acids in a non-reabsorbable form in the  
32 gastrointestinal tract.

33

1 15. A compound of general formula II



II

wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$  and  $X$  are as defined in claim 1; and

$R_8$ ,  $R_9$  and  $R_{10}$  independently comprise  $C_{1-8}$  alkyl or phenyl.

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